

Pulmonary Manifestations of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic systemic disease of unknown etiology characterized by articular involvement, extra-articular involvement, and the presence of serum rheumatoid factor. In RA, there is a symmetric and persistent inflammation of the synovial tissue, usually involving the peripheral joints. Patients with RA who have high titers of rheumatoid factor (ie, autoantibodies to the Fc component of immunoglobulin G) are most likely to have extra-articular manifestations of their disease, including rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications.

The prevalence of RA in the United States is approximately 0.8% of the population. All races are affected,¹ and women are 3 times more likely than men to be affected. Onset of illness most frequently occurs during the fourth and fifth decade of life. The extra-articular manifestations of RA can occur at any age after onset. Given the high prevalence of RA and the variety of its manifestations, the American College of Rheumatology in 1987 developed revised criteria for the classification of RA (**Table 1**). Diagnosing RA in patients using these criteria has a sensitivity of 91% to 94% and a specificity of 89%.^{1,2}

Because of the potentially life-threatening nature of some of the pulmonary complications of RA, this article will review the involvement of the respiratory system in the disorder. The differential diagnosis and management of pulmonary complications will be discussed, as will other common issues that clinicians should be aware of in order to promptly diagnose and treat their patients with RA.

PULMONARY MANIFESTATIONS

The pulmonary manifestations of RA were first de-

scribed in 1948, when Ellman and Ball recognized diffuse pulmonary fibrosis in three patients with RA.³⁻⁶ Since that time, many authors have described the association between various pulmonary complications and RA.^{1,3,6,7}

Although it is difficult to assess the true prevalence of lung disease in cases of RA, the clinical features that predispose patients to lung involvement are well known and include middle age, male gender, severe destructive arthritis, highly elevated titers of rheumatoid factor, and the presence of subcutaneous nodules or other extra-articular rheumatoid manifestations.^{7,8} The diverse pulmonary manifestations of RA (**Table 2**) are usually divided into 7 major categories: (1) pleural effusion, (2) nodular lung disease, (3) diffuse interstitial fibrosis, (4) pulmonary vasculitis, (5) alveolar hemorrhage, (6) obstructive pulmonary disease, and (7) infections.¹⁻¹⁴

Pleural Effusion

The most common pulmonary manifestation of RA is pleural effusion.^{3,4,7} Pleural effusions are often discovered on routine chest radiographs of patients with RA. Post-mortem studies have revealed that nearly 50% of patients with RA have effusions.^{1,3,4} This complication is at times asymptomatic, possibly because physical activity in these

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Table 1. American College of Rheumatology Revised Criteria for Diagnosing Rheumatoid Arthritis

Guidelines for classification

- At least 4 of 7 criteria are required to classify a patient as having rheumatoid arthritis
- Patients with 2 or more clinical diagnoses are not excluded

Criteria

- Morning stiffness*
- Arthritis of 3 or more joints*
- Arthritis of hand joints*
- Symmetric arthritis*
- Rheumatoid nodules
- Serum rheumatoid factor
- Radiographic changes

*Must be present for at least 6 weeks.

patients is limited.^{1,7} In patients with RA who have pleural effusions, however, respiratory symptoms such as pleuritic pain, dyspnea, and (less commonly) cough can be present.¹² In up to 25% of these patients, pleural effusions will precede or occur simultaneously with the onset of joint disease.^{3,7,12} These effusions can be unilateral or bilateral and can resolve completely, recur, increase in size, and persist for many months.^{3,7,8,12,13} Most often, pleural effusions in patients with RA consist of exudates containing mononuclear cells. Results of pleural biopsy typically show a higher concentration of rheumatoid factor than is present in the serum, high concentrations of protein and lactate dehydrogenase, a very low concentration of glucose, decreased complement activity, a low pH, and an elevated polymorphonuclear leukocyte count (**Table 3**)^{3,5,7,8,13}; these polymorphonuclear leukocytes typically contain dense black granules (RA cells) that release rheumatoid factor when disintegrated.

Asymptomatic pleural effusions need not be treated. For patients with RA who have symptomatic pleural effusions, various studies have reported that repeated thoracentesis, pleurodesis (using either talc, bleomycin, or tetracycline), and administration of corticosteroids can be beneficial.^{2-4,7} However, these techniques have not been shown to provide consistent benefit. Therapy directed at the underlying rheumatoid disease might be more helpful.²

Nodular Lung Disease

Pulmonary nodules in patients with RA were first described by Caplan in 1953, after he discovered the

characteristic multiple bilateral nodules on chest radiographs of coal miners with RA.^{3,7} These necrobiotic pulmonary nodules are rare and usually asymptomatic, although they can cause coughing and, occasionally, hemoptysis. Pulmonary nodules can appear before, with, or after the onset of RA. They are more commonly multiple than single, vary from a few millimeters to several centimeters in diameter, and tend to involve both lungs (**Figure 1**).^{3,7} These nodules usually occur at the periphery of the lung, just beneath the pleura, and occasionally can cause bronchopleural fistula, pneumothorax, and abscess formation or cavitation leading to hemoptysis (because capillary vessels of the lungs are involved). The natural history of pulmonary nodules is variable, with nodules remaining static, increasing in size and number, resolving, or undergoing malignant transformation.^{1,3,7,8,12,13,15}

The management of nodular lung disease primarily consists of observation to detect changes in the size or shape of nodules. Transbronchial biopsy or transthoracic needle aspiration might be necessary to rule out other pathologies (eg, malignancy). Complications resulting from the nodules (eg, hemoptysis, bronchopleural fistula, pneumothorax) should be treated directly.^{3,7}

Diffuse Interstitial Fibrosis

Diffuse interstitial fibrosis has been described in approximately 40% of patients with RA.^{3,7} The disorder initially is characterized by chronic inflammatory changes in the alveolar walls and the presence of large mononuclear cells in the alveolar spaces. As the disease progresses, there is a tendency to fibrosis with obliteration of some of the alveoli and dilatation of the bronchioles.¹² The pulmonary areas primarily affected are the bases of the lungs in the early stages of the disease and the apices of the lung in more advanced stages.

Diffuse interstitial fibrosis occurs mostly in patients who have subcutaneous nodules and high titers of rheumatoid factor.^{3,7} Symptoms include progressive dyspnea on exertion and a productive cough. Examination of affected patients can reveal an increased respiratory rate, clubbing, and crepitations, particularly at the bases of the lungs.¹² Chest radiographs typically show a reticulated pattern with progression to a fine nodularity and honeycomb fibrosis.⁷

Using bronchoalveolar lavage, Kolarz and colleagues showed that in patients with RA who have lung involvement, including interstitial fibrosis, there is a statistically significant increase in the number of lymphocytes, especially activated (DR+)T(CD3+) helper and CD4+ cells.^{16,17} They further reported that this increase results in a significantly diminished percentage of

Table 2. Pulmonary Complications of Rheumatoid Arthritis

Manifestation	Signs and Symptoms	Clinical Findings
Pleural effusion	Usually asymptomatic but can involve pleuritic pain, dyspnea, and cough	Decreased bibasilar breath sounds
Nodular lung disease	Usually asymptomatic but can involve cough and hemoptysis	Localized wheezing on occasion
Diffuse interstitial fibrosis	Dyspnea on exertion and productive cough	Increased respiratory rate, clubbing, and crepitations at base of lung(s)
Pulmonary vasculitis	Dyspnea	Bilateral basilar rales
Alveolar hemorrhage	Hemoptysis	Decreased bibasilar breath sounds, consolidation, rales
Obstructive pulmonary disease	Shortness of breath	Rales and high midinspiratory wheezes
Infections	Dyspnea, cough, fever, yellow sputum	Consolidation, rhonchi, rales

alveolar macrophages, B(CD21+)-lymphocytes, and T-suppressor (CD8+) cells, as well as an increased CD4/CD8 ratio.¹⁶ The clinical significance of this study involves the role these inflammatory cells play in RA.

The prognosis for patients with RA who have interstitial fibrosis is poor. Therapeutic success depends on the amount of active inflammation or fibrosis present when treatment begins. Medications typically given to patients with RA and interstitial fibrosis include corticosteroids, azathioprine, and other immunomodulating agents.^{3,7}

Pulmonary Vasculitis

Although the most frequent site of vascular inflammation in patients with RA is the skin, vasculitis can affect almost any organ system. Pulmonary vasculitis, one of the least common pulmonary manifestations of RA, is seen in patients with severe RA and high titers of rheumatoid factor and can occur in either a widespread or a limited manner. The limited form is particularly common in patients who are white, whereas it is very uncommon in patients of African ancestry. On rare occasions, pulmonary hypertension resulting from pulmonary vasculitis can occur. The diagnosis of pulmonary vasculitis requires histologic evidence of vasculitis and hemodynamic measurements (eg, of pulmonary artery pressures).^{1,3,7}

Some of the pharmacologic agents that have been used to treat RA-related pulmonary vasculitis include corticosteroids and cytotoxic drugs (eg, methotrexate, azathioprine, cyclophosphamide). Penicillamine and gold salts are also administered to patients with this condition,¹⁸ with variable results.

Table 3. Pleural Fluid Findings in Patients with Rheumatoid Arthritis

Type of fluid: exudative
Complement level: low
Glucose level: low (< 30 mg/dL)
Lactate dehydrogenase level: high
pH: low (< 7.2)
Protein level: high (> 4 g/dL)
Polymorphonuclear leukocyte count: high, with RA cells and mononuclear cells
RF level: higher than serum RF level

RA = rheumatoid arthritis; RF = rheumatoid factor.

Alveolar Hemorrhage

Alveolar hemorrhage (AH) is another pulmonary manifestation of RA. Pulmonary AH involves diffuse bleeding from the pulmonary vasculature, resulting in blood-filled alveoli. This occurrence leads to a classic triad of hemoptysis, diffuse infiltrates, and anemia. From a pathologic standpoint, AH can be described as an acute or chronic condition. In acute cases, erythrocytes and fibrin fill the air spaces; hemosiderin-laden macrophages are often present. Capillaritis limited to the alveolar wall is observed in as many as 88% of patients with RA who have acute AH.

Radiographic findings in RA-related AH depend on the extent of the bleeding and the elapsed time since the bleeding last occurred. Characteristically, chest radiography and computed tomography (**Figure 2**)



Figure 1. Chest radiograph of a 48-year-old man with rheumatoid arthritis and nodular lung disease showing pulmonary nodules involving both lungs.

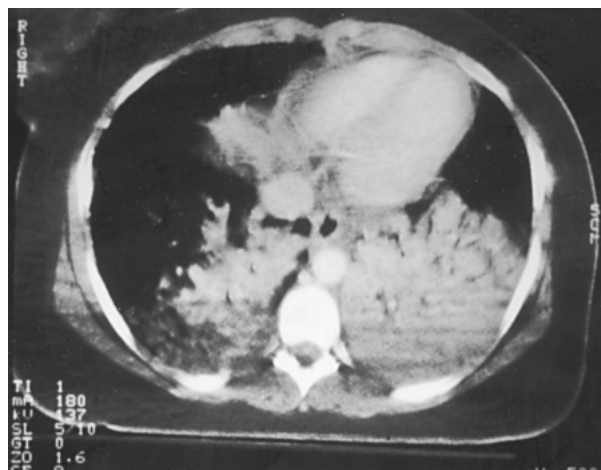


Figure 2. Computed tomography scan of a patient with rheumatoid arthritis and an episode of hemoptysis showing diffuse patchy alveolar infiltrates.

demonstrate diffuse or focal patchy alveolar infiltrates. The distribution is usually symmetric and perihilar, with infiltrates typically not seen on the apices or costophrenic angles.¹⁰

Measurement of the diffusing capacity of the lung for carbon monoxide (DLCO) can help in the diagnosis of AH in patients with RA. The DLCO will be increased as a result of the carbon monoxide binding to the blood in the alveoli.^{19,20}

Obstructive Pulmonary Disease

The finding of airway obstruction in 38% to 68% of patients with RA in some series has prompted the suggestion that airway disease might be the most prevalent pulmonary manifestation of RA.²¹ Patients with RA and airway obstruction typically report a rapid development of shortness of breath on initial presentation; examination usually reveals rales and high-pitched inspiratory wheezes. Chest radiographs depict hyperinflated lungs but no other abnormalities.²² Parenchymal involvement of the lung in patients with RA, although possibly not evident on radiographs, is suggested by the finding of a higher incidence of interstitial pneumonia in autopsies of such patients. The primary abnormality discovered in postmortem studies is a fibrous narrowing or obliteration of the airways, measuring 1 to 6 mm in diameter.^{22,23}

In general, lung function tests of patients with RA-related airway obstruction show airflow obstruction that is most marked when respiratory volumes are low and trapping of air occurs. The mean forced expiratory volume in 1 second and forced vital capacity are reduced, even more so if the tested patient smokes. The

maximum midexpiratory flow rate likewise is reduced. As early as 1976, Collins and colleagues showed that patients with RA have low midexpiratory flow rates.²⁴ Moreover, these investigators showed that cigarette smokers with RA have significantly lower midexpiratory flow rates than do nonsmokers with RA. The results of this study strongly suggest that the combination of tobacco smoking and RA is associated with a much higher prevalence of obstructive pulmonary disease.²⁴

Several studies also have shown that the peak respiratory flow rate is significantly reduced in patients with RA and airway obstruction.^{3-5,18} Another commonly seen abnormality of lung function is an abnormal ventilation/perfusion ratio, with a consequent alteration in arterial blood gas findings.²¹⁻²⁶

Infections

Infections are a persistent problem in the clinical course of RA. Both common and uncommon pathogens are found in patients with the disorder. The frequency of infection increases with the administration of corticosteroids as immunosuppressive agents.²⁷ An immunologic disturbance might antedate the development of RA, a possibility that would have bearing on theories of an infectious etiology of this disease.³

In the early 1970s, several investigators who were searching extensively for etiologic factors associated with RA found that 21.8% of patients with RA had a lung infection, whereas only 10.6% of controls without a rheumatic disease had such an infection.²⁷ Aronoff and colleagues reported in their classic study that patients with RA and lung lesions had a high incidence

of bronchitis and bronchiectasis.²⁸ Acute and chronic bronchitis, bronchiectasis, and pneumonia have been shown to occur more frequently in patients with RA than in controls with degenerative joint disease.¹³ An increased prevalence of massive fibrosis and tuberculosis has been reported in children with RA, compared to controls.²⁹

Huskisson and Hart described in 1972 the major role played by infection in the deterioration and death of patients with RA.³⁰ In 1977, Geddes and colleagues suggested that abnormal sensitivity to airway inflammation from chemical or viral agents, with a resultant obliterative bronchiolitis, might occur in patients with RA.²² In 1981, Herzog and colleagues described a case of a patient with RA who had acute bronchiolitis (without obstructive airway disease) and linear deposition of IgG in alveolar walls.³¹

CONCLUSION

RA is a disorder characterized by diverse chronic manifestations and the need for long-term treatment. RA can affect multiple organs and tissues, including the lungs. Pulmonary complications of RA include pleural effusion, nodular lung disease, diffuse interstitial fibrosis, pulmonary vasculitis, alveolar hemorrhage, obstructive pulmonary disease, and lung infections. In order to provide optimal treatment, physicians must always consider the possibility of pulmonary manifestations when evaluating patients with RA. **HP**

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